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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/361,576	07/27/1999	BRENT R. STOCKWELL	2001180-0028	5706

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EXAMINER	
STEELE, AMBER D	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/361,576	STOCKWELL ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006 and 27 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-59,63,64,66-69,71,76,77,80,83 and 85-110* is/are pending in the application.

4a) Of the above claim(s) *58 and 105-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57, 59, 63-64, 66-69, 71, 76-77, 80, 83, 85-104, and 108-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner for the present application has changed. However, the Technology Center (TC1600) and the Art Unit (AU1639) remain the same.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on April 27, 2006 and October 31, 2006 have been entered.

Status of the Claims

3. The amendment to the claims received on October 31, 2006 amended claims 57-58, 77, 80; canceled claims 1-56, 60-62, 65, 70, 72-75, 78-79, 81-82, 84; and added new claims 108-110.

Claims 57-59, 63-64, 66-69, 71, 76-77, 80, 83, 85-110 are currently pending.

Claims 57, 59, 63-64, 66-69, 71, 76-77, 80, 83, 85-104, and 108-110 are currently under consideration.

Election/Restrictions

4. Applicant's election by original presentation of a method for screening one or more test compounds is traversed in the reply filed on April 27, 2006 and is acknowledged. The traversal is on the ground(s) that claim 58 encompasses all the steps of claim 57 yet a plurality of reagents are utilized in order to generate a fingerprint and a search burden does not exist. This is not

found persuasive because Group B (claims 58 and 105-107) requires the step of recording the effects of each test compound on the plurality of intracellular biological or chemical processes, thereby establishing a functional fingerprint for each test compound which is not found in the method of Group A. In addition, Group A requires assessment of the ability of the test compounds to modify a single polypeptide whereas Group B requires assessing multiple polypeptide modifications. A search burden exists due to the different classification (e.g. class and/or subclass) wherein Group A is classified in class 435, subclass 7.1 and Group B is classified in class 530, subclass 412.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 58 and 105-107 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 27, 2006.

Priority

6. The present application claims priority to provisional applications 60/094,305 filed July 27, 1998; 60/131,765 filed April 30, 1999; and 60/137,039 filed June 1, 1999.

Claim Objections

7. Claims 59, 63, 64, 69, 71, 76, 83, 85-88, 91-104, and 110 are objected to because of the following informalities: the claims are dependent on claim 58 which is withdrawn as being drawn to a nonelected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 109 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Support for the claim limitation of "wherein the antibody associates intracellularly with the polypeptide prior to posttranslational modification" was not found in the present specification.

10. Claims 57, 59, 63-64, 66-69, 71, 76-77, 80, 83, 85-104, 108-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A nexus between method step (b) and method step (c) of claim 57 is missing in certain embodiments. For example, method step (b) states that "at least some of the reaction vessels" will receive an antibody, but method step (c) requires assaying for association between the antibody and the biological component. Therefore, how would one of skill in the art perform method step (c) in the reaction vessels without antibody? Thus, the scope of the presently claimed invention would not be readily ascertained by one of skill in the art due to the missing nexus between method step (b) and method step (c).

11. Claims 57, 59, 63-64, 66-69, 71, 76-77, 80, 83, 85-104, 108-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation of claim 57 that "an antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on post-translational modification of the polypeptide" is indefinite. For example, are the biological component and the polypeptide the same or different, is the biological component the post-translational modification (e.g. phosphate, etc.), is the biological component a peptide, protein, nucleic acid, etc.? Therefore, one of skill in the art would not be able to determine the scope fo the presently claimed invention.

Withdrawn Rejections

10. The rejection of claims 57, 59-60, 63-71, 76-81, 83, and 85-104 under 35 U.S.C. 103(a) as being unpatentable over Stylli et al. (US Patent 5,985,214) and Photiou et al. (*European Journal of Cancer*, **3/1997**, 33(3), pgs. 463-470) is withdrawn due to the claim amendments received on October 31, 2006 (post-translational modifications). The rejection of claims 72-75 under 35 U.S.C. 103(a) as being unpatentable over Stylli et al. (US Patent 5,985,214) and Photiou et al. (*European Journal of Cancer*, **3/1997**, 33(3), pgs. 463-470) as applied to claims 57, 59-60, 63-71, 76-81, 83, and 85-104 and further in view of Walsh, (US Patent 5,990,092) is withdrawn due to the claim amendments received on October 31, 2006 (post-translational modifications).

Present Invention

11. The presently claimed invention is drawn to a method comprising: (a) introducing a plurality of cells and one or more test compounds into a plurality of reaction vessels, (b) introducing into at least some of the reaction vessels an antibody that associates intracellularly with a biological component indicates a post-translational modification of a polypeptide has occurred, and (c) assaying for association between the antibody and the biological component in the reaction vessels.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 57, 59, 69, 71, 76-77, 80, 83, 85-89, 91-104, 108 are rejected under 35 U.S.C. 102(e) as being anticipated by Harris et al. U.S. Patent 6,400,487 (effective filing date of March 16, 1998) alone or as evidenced by Garyantes U.S. Patent 6,565,813 (effective filing date of February 4, 1998) regarding reaction vessel parameters.

For present claims 57, 59, 69, 71, 76-77, 80, 83, 85-89, 91-104, 108, Harris et al. teach methods for high throughput screening of chemical compounds via cell-based assays comprising (a) plating cells in a 96 well plate and adding chemical compounds, (b) permeabilizing the cells and adding antibody (e.g. intracellular antibody staining), and (c) assaying for the association of the antibody with the antibody target wherein posttranslational modifications are determined

including phosphorylation. In addition, Harris et al. teach washing steps, an aspirate-dispense-wash cycle (i.e. removing unassociated antibody); fluorescence; vertebrate cells (i.e. eukaryotic, mammalian, human); synthetic chemical compounds from combinatorial libraries, chemical compounds including amino acids, nucleic acids, etc.; microtiter plates holding various volumes, having various well numbers and sizes, and with various dimensions (please refer to Garyantes entire specification particularly abstract; Figures 1, 8B; columns 1-3, 7-12, 14, 19, 21-26; Examples 1-5). Please refer to entire specification of Harris et al. particularly abstract; Figures 15A-28A; columns 1-2, 4-9, 17-22, 27, 29, 33-34; Examples. Therefore, the presently claimed invention is anticipated by the teachings of Harris et al.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 57, 59, 64, 66-67, 69, 71, 76-77, 80, 83, 85-104, 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Darznkiewicz et al. U.S. Patent 7,070,943 (effective filing date February 25, 1998) and Dower et al. U.S. Patent 5,639,603 filed June 17, 1997 alone or as evidenced by Garyantes U.S. Patent 6,565,813 (effective filing date of February 4, 1998) regarding reaction vessel parameters.

For present claims 57, 59, 64, 66-67, 69, 71, 76-77, 80, 83, 85-88, 102-103, 108, Darznkiewicz et al. teach a method of screening chemical compounds/drugs for antiproliferative and antineoplastic activity comprising (a) plating cells and adding chemical compounds, (b)

permeabilizing cells and adding antibody to detect phosphorylated proteins intracellularly, and (c) assaying for antibody binding to phosphorylated proteins via flow cytometry. In addition, Darznkiewicz et al. teach washing unbound antibody away; secondary antibodies; fluorescence detection; adherent cells; human PBMCs, cell lines; synthetic drugs. Please refer to the entire specification particularly abstract; Figures 1-16; columns 1-6, 9-14, 17, 19; Examples 1-3.

However, Darznkiewicz et al. does not teach 96 reaction vessels.

For present claims 57 and 89-104, Dower et al. teach methods of high throughput compound screening comprising (a) plating cells and adding test compounds, (b) adding antibodies that bind to various targets and indicate activity including phosphorylation, and (c) assaying for antibody binding via flow cytometry or ELISA wherein the method utilizes a combinatorial chemical library covalently bound to a solid support which can be cleaved from the solid support and 96 well plates (please refer to entire specification particularly columns 4, 7, 9, 29-33, 36-42; Example 1). Furthermore, the features of the specific volume of the reaction vessel, reaction vessel format, and reaction vessel dimensions are either specifically described by the reference, or constitute obvious variations in parameters which are routinely modified in the art, and which have not been described as critical to the practice of the invention (please refer to Garyantes entire specification particularly abstract; Figures 1, 8B; columns 1-3, 7-12, 14, 19, 21-26; Examples 1-5).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of screening chemical compounds/drugs for antiproliferative and antineoplastic activity taught by Darznkiewicz et al. with the 96 reaction vessel and chemical compound library taught by Dower et al.

One having ordinary skill in the art would have been motivated to do this because Dower et al. teach that high throughput screening (e.g. 96 well format) of collections of chemically synthesized molecules and of natural products is critical for the development of new pharmacological agents (please refer to columns 2-3 of Dower et al.).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method of screening chemical compounds/drugs for antiproliferative and antineoplastic activity taught by Darznkiewicz et al.with the 96 reaction vessel and chemical compound library taught by Dower et al. because Dower et al. teach high throughput screening of chemical compounds (please refer to Example 1) and Darznkiewicz et al. teach screening of a drug utilizing intracellular antibody staining of phosphorylated proteins (please refer to Example 3).

Therefore, the modification of the method of screening chemical compounds/drugs for antiproliferative and antineoplastic activity taught by Darznkiewicz et al. with the 96 reaction vessel and chemical compound library taught by Dower et al. render the instant claims *prima facie* obvious.

16. Claims 57, 59, 63-64, 66-69, 71, 76-77, 80, 83, 85-89, 91-104, 108, and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godowski et al. WO 95/14930 (published June 1, 1995) and Ochoa et al. U.S. Patent 5,658,744 issued August 19, 1997 alone or as evidenced by Garyantes U.S. Patent 6,565,813 (effective filing date of February 4, 1998) regarding reaction vessel parameters.

For present claims 57, 59, 63-64, 67-69, 71, 76-77, 80, 83, 85-87, 91-104, 108, and 110, Godowski et al. teaches high throughput screening assays comprising (a) plating cells in 96 well plates and adding ligands/substrates/analyte (i.e. test compounds), (b) adding an antibody that detects post-translational modifications including phosphorylation, and (c) assaying for antibody detection of posttranslational modifications. In addition, Godowski et al. teaches horseradish peroxidase (HRPO or HRP) labeled antibodies, secondary antibodies; various microtiter plates with various number of wells, various dimensions, and maximum volumes of 250µl (please refer to Garyantes entire specification particularly abstract; Figures 1, 8B; columns 1-3, 7-12, 14, 19, 21-26; Examples 1-5); human cell lines; adherent cells; washing to remove excess or unbound antibody; fluorescence, chemiluminescence; natural ligands; synthetic ligands. Please refer to the entire specification including abstract; pages 3, 5-8, 13-15, 17-20, 30-33, 35-37, 44-46, 49; Examples. Furthermore, the features of the specific volume of the reaction vessel, reaction vessel format, and reaction vessel dimensions are either specifically described by the reference, or constitute obvious variations in parameters which are routinely modified in the art, and which have not been described as critical to the practice of the invention.

However, Godowski et al. does not teach intracellular antibody staining.

For present claims 57 and 66, Ochoa et al. teach methods of screening for agents that alter immunosuppression and methods of identifying the immune status of patients comprising (a) plating cells in 96 well plates wherein agents can be added, (b) permeabilizing cells and adding antibodies that bind posttranslationally modified proteins including phosphorylated proteins, and (c) assaying for antibody binding via fluorescence, chemiluminescence, or radioactivity. Please refer to entire specification particularly columns 6-8; Example 3.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to alter the high throughput screening assay of Godowski et al. with the intracellular staining taught by Ochoa et al.

One having ordinary skill in the art would have been motivated to do this because some cellular markers which can be posttranslationally modified are intracellular (e.g. CD3 zeta chain; only 9 amino acids on the cell surface as opposed to 113 amino acids in the cytoplasm; please refer to Example 3 of Godowski et al.). In addition, utilization of intracellular staining would not require lysing cells and transferring samples to a separate plate as taught by Godowski et al. and thus reduce the number of steps and time in a high throughput assay and Ochoa et al. teach that the results from cell lysates in an ELISA format and intracellular antibody staining provide comparable results (please refer to Examples 2-3 and Tables 1-3 of Ochoa et al.).

One of ordinary skill in the art would have had a reasonable expectation of success in the modification of the high throughput screening assay of Godowski et al. with the intracellular staining taught by Ochoa et al. because of the results provided by Ochoa et al. showing intracellular antibody staining (please refer to Example 3 and Table 3).

Therefore, the modification of the high throughput screening assay of Godowski et al. with the intracellular staining taught by Ochoa et al. render the instant claims *prima facie* obvious.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
March 14, 2007

MARK L. SHIBUYA
PRIMARY EXAMINER